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Clinical Investigation

Progression of Renal Impairment and Chronic Kidney Disease in Chronic Heart Failure: An Analysis From GISSI-HF

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ABSTRACT

Background: Data on the natural change in renal function in patients with chronic heart failure (HF) are limited.

Methods and Results: Estimated glomerular filtration rate (eGFR) was assessed over 36 months in 6934 patients included in the GISSI-HF study. Associations from baseline, changes in renal function, and occurrence of cardiovascular death or HF hospitalization were assessed. Mean age was 67 years, mainly men (78%), and mean eGFR was 68 mL • min^{-1} • 1.73 m^{-2}. Change in eGFR in the 1st year was −1.5 ± 16 mL • min^{-1} • 1.73 m^{-2}, and over 36 months it was −3.7 ± 18 mL • min^{-1} • 1.73 m^{-2}. Over the latter period, only 25% deteriorated ≥1 Kidney Disease Outcomes Quality Initiatives (KDOQI) class of chronic kidney disease (CKD). Fifteen percent of patients had >15 mL • min^{-1} • 1.73 m^{-2} decrease in eGFR in the 1st 12 months. Lower eGFR was associated with outcome: hazard ratio (HR) 1.10, 95% confidence interval (CI) 1.08–1.10 ($P < .001$) per 10 mL • min^{-1} • 1.73 m^{-2} decrease, as well as every 10 mL • min^{-1} • 1.73 m^{-2} decrease over the 1st year (HR 1.10, 95% CI 1.04–1.17; $P < .001$). A deterioration in eGFR >15 mL • min^{-1} • 1.73 m^{-2} in the 1st year showed the highest risk of events (HR 1.22, 95% CI 1.10–1.36; $P < .001$).

Conclusions: Mean decrease in renal function over time in patients with chronic HF was modest. Only 25% deteriorated ≥1 KDOQI class of CKD after 3 years. Any decrease in eGFR over time was associated with strongly increased event rates. (*J Cardiac Fail 2017;23:2–9*)

Key Words: Renal function, chronic heart failure, prognosis, chronic kidney disease.

Renal function as estimated by glomerular filtration rate (eGFR) generally declines ~0.5-1.0 mL • min^{-1} • 1.73 m^{-2} per year.[1] Any decline in renal function, or the presence of a reduced GFR at any point in time, has been associated with worse outcomes in multiple populations.[2] This is also the case for renal impairment in chronic heart failure (HF), which is strongly associated with increased event rates. In a recent meta-analysis of >1 million subjects, the presence of chronic kidney disease (CKD; usually defined as eGFR <60 mL • min^{-1} • 1.73 m^{-2}) was associated with a >2-fold increase in all-cause mortality rates.[3] Additionally, recent research has shown that a deterioration of renal function, or more importantly, an increase in serum creatinine, is associated with a further increase in mortality.[3,4] However, the circumstances during which this "worsening renal function" (WRF) develops seem far more important than the occurrence of WRF itself.[5] Although multiple reports focused on these changes, most evaluated WRF during a short follow-up time, only limited reports evaluated the progression of CKD or deterioration of renal function (ie, GFR) over a longer period of time. In fact, limited data are available on the "normal" decline in renal function in patients with HF. In the present analysis from the GISSI-HF (Effects of n-3 Polyunsaturated Fatty

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Acids [PUFA] and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic Congestive Heart Failure; Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca study, we investigated the "natural course" of change in GFR, the progression of stages of CKD, and the associated prognosis in patients with chronic HF.

Methods

GISSI-HF was a randomized, double-blinded, placebo-controlled, multicenter study that enrolled 6975 patients with clinical evidence of HF (New York Heart Association [NYHA] functional class II–IV). Patients were randomly assigned in a nested design to 1 g daily n-3 PUFA or placebo, and for those who were eligible, to 10 mg daily rosuvastatin or placebo. The design and results of the main trial have been published.[6–8] Patients with a baseline serum creatinine >2.5 mg/dL (222 μmol/L) were excluded from the rosuvastatin substudy.

GFR and CKD

Estimated GFR was calculated with the use of the simplified Modification of Diet in Renal Disease (sMDRD) formula at baseline and 1, 3, 6, 12, 24, and 36 months. Serum creatinine was available in 6934, 6159, 6061, 5715, 4956, 4104 patients at randomization, 3 months, 6 months, 1 year, 2 years, and 3 years, respectively. This formula was selected because it was used in earlier analyses from GISSI-HF. CKD was classified with the use of the Kidney Disease Outcomes Quality Initiatives (KDOQI) classification (all in mL • min^{-1} • 1.73 m^{-2}): eGFR ≥90, class I; eGFR <90 and ≥60, class II; eGFR <60 and ≥30, class III; eGFR <30 and ≥15, class IV; and finally eGFR <15, class V. Early change in eGFR was determined as the change in eGFR during the 1st year of follow-up and was categorized in the following groups: >15, 15-10, 5–10, and 0–5 mL • min^{-1} • 1.73 m^{-2} decrease and >0 mL • min^{-1} • 1.73 m^{-2} increase in eGFR.

Clinical Outcome

The primary outcome was the 1st occurrence of either cardiovascular (CV) death or HF hospitalization as adjudicated in the original GISSI-HF study. Secondary outcome included each individual component: CV death or HF Hospitalization.

Statistical Analysis

Categoric variables are presented as percentages, while continuous variables are presented as mean and SD or as median and interquartile range (IQR).

Categoric variables were compared by means of the chi-square test and continuous variables by means of analysis of variance or Kruskal-Wallis test. Change in renal function was assessed with the use of repeated-measures mixed-effects modeling, setting all baseline variables as fixed effects, patient identification as random effects, and time as the within-subject variable. This method uses all available data, including baseline data and data of deceased subjects, that are available until death. Interaction analysis was used to assess possible effect modification of baseline characteristics on the slope of eGFR over time. All variables of relevant clinical interest were included in the multivariable Cox model to identify the effect of eGFR on the primary end point and included age, sex, body mass index, NYHA functional class, etiology of HF, left ventricular ejection fraction (LVEF), heart rate, systolic and diastolic blood pressures, serum potassium, triglycerides, history of hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease, and the use of concomitant medication (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, spironolactone, or statins). Linearity of eGFR was tested by means of restricted cubic spline transformation. For the association between early change in eGFR and outcome, patients with events in the 1st year were excluded from the analysis. A P value of <.05 was considered to be statistically significant. All tests were two-sided. Analyses were performed with R[9] and the packages Rms (regression modeling strategies; Frank E. Harrell Jr [2014]; R package version 4.2-0; http://CRAN.*R*-project.org/package=rms) and Reporttools (Kaspar Rufibach [2009]; Report tools: R Functions to Generate LaTeX Tables of Descriptive Statistics, Journal of Statistical Software, Code Snippets, 31[1]; http://www.jstatsoft.org/v31/c01/).

Results

Baseline Characteristics and Baseline Renal Function/CKD

A total of 6934 patients had data on baseline serum creatinine available. The patients were mainly male (78%), with an overall mean age of 67 years and a mean LVEF of 33%. Baseline eGFR was 68 mL • min^{-1} • 1.73 m^{-2}, which was higher in men (70 mL • min^{-1} • 1.73 m^{-2}) than in women (62 mL • min^{-1} • 1.73 m^{-2}; $P < .001$).

Change in Renal Function Over Time

The mean change in eGFR over time in the entire study population is depicted in Fig. 1. In the first 12 months, the mean change in eGFR was −1.5 ± 16 mL • min^{-1} • 1.73 m^{-2}, whereas it was 3.7 ± 18 mL • min^{-1} • 1.73 m^{-2} over the entire study period of 36 months. This translated into a median decline in eGFR of 2.57 mL • min^{-1} • 1.73 m^{-2}/year. A total of 842 patients (14.8%) had a decrease of >15 mL • min^{-1} • 1.73 m^{-2} in the 1st year. Prevalence of −15 to −5 mL • min^{-1} • 1.73 m^{-2} in the 1st year was 19.8%; −5 to +5 mL • min^{-1} • 1.73 m^{-2}, 31.3%; +5 to +15 mL • min^{-1} • 1.73 m^{-2}, 23.5%; and >15 mL • min^{-1} • 1.73 m^{-2} increase in 1 year 10.5% . Table 1 presents the baseline characteristics when stratified for these changes in eGFR.

Among subsets of patients, we found limited interactions between the slope of eGFR over time and the presence or absence of specific conditions. Specifically, we found no evidence of interaction between time and the association with the slope of

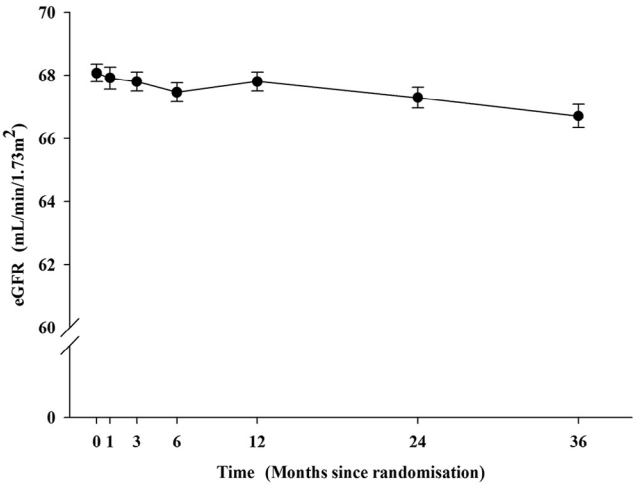

Fig. 1. Change in estimated glomerular filtration rate (eGFR) in patients with creatinine/eGFR available at all time points.

eGFR for diabetes, hypertension, atrial fibrillation, age, NYHA functional class, and most therapies, including randomized rosuvastatin or n-3 PUFA treatment. We did find significant interactions for the presence or absence of COPD (steeper decline in eGFR when COPD was present), loop diuretic use (earlier and steeper decline of eGFR with loop diuretic use, overall similar decline after 36 months), and evidence of impaired renal function at baseline (Fig. 2). For the latter, we found that patients with relatively preserved renal function (higher eGFR or lower creatinine) had steeper decline of eGFR over time compared with those with already compromised renal function.

Progression of CKD

At baseline, the distribution of patients according to KDOQI stages of CKD was class I, 14.9%; class II, 47.5%; class III, 34.3%; class IV, 3.1%; and class V, 0.2%. In the 1st 12 months, overall 19% of patients deteriorated ≥1 stage of CKD and 14% of patients improved ≥1 stage (67% remained stable). After 36 months of follow-up, the distribution of patients according to KDOQI stages had changed to class I, 14.6%; class II, 46.6%; class III, 36.0%; class IV, 3.9%; and class V, 0.4%. Overall, 25% of patients had deteriorated ≥1 class and 14% had improved ≥1 class.

Renal Function, Changes in Renal Function, and Clinical Outcome

In this study, a total of 3756 patients reached the primary end point of either CV death of HF hospitalization. Excluding the subjects who died, the censored times were in the range 0–70 months (median ~50 mo, IQR 41–55 mo). Lower baseline eGFR was associated with increased event rates (hazard

Table 1. Baseline Characteristics According to Change in Estimated Glomerular Filtration Rate (eGFR; mL • min^{-1} • 1.73 m^{-2}) Over the First Year

	>15 Decrease	5–15 Decrease	−5 to +5 (Stable)	5–15 Increase	>15 Increase	*P* Value
n (%)	599 (14.8)	1124 (19.8)	1785 (31.3)	1338 (23.5)	842 (10.5)	
Age, y	64 ± 11	67 ± 11	68 ± 10	68 ± 10	66 ± 11	<.001
Sex (male, %)	78	79	78	78	79	.97
BMI (kg/m^2)	28 ± 5	27 ± 4	27 ± 4	27 ± 4	27 ± 5	.39
NYHA III–IV (%)	35	30	33	35	34	.09
Ischemic HF (%)	42	47	51	51	47	<.001
LVEF, %	33 ± 8	33 ± 8	33 ± 8	33 ± 9	33 ± 8	.76
HR, beats/min	73 ± 14	72 ± 13	72 ± 13	71 ± 13	73 ± 13	.04
SBP, mm Hg	126 ± 18	126 ± 18	128 ± 18	127 ± 18	126 ± 17	.01
DBP, mm Hg	77 ± 10	77 ± 10	77 ± 10	77 ± 10	77 ± 10	.98
Potassium, mmol/L	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	<.001
Triglycerides, mg/dL	147 ± 84	154 ± 99	155 ± 107	145 ± 87	139 ± 90	<.001
Serum creatinine, mg/dL	1.2 ± 0.6	1.2 ± 0.4	1.3 ± 0.5	1.1 ± 0.4	0.9 ± 0.2	<.001
eGFR, mL • min^{-1} • 1.73 m^{-2}	66 ± 21	64 ± 19	65 ± 21	70 ± 19	88 ± 28	<.001
KDOQI classification (%)						<.001
eGFR ≥90 mL • min^{-1} • 1.73 m^{-2}	11	8	11	14	41	
eGFR 60 – 89 mL • min^{-1} • 1.73 m^{-2}	49	51	45	56	46	
eGFR 30 – 59 mL • min^{-1} • 1.73 m^{-2}	36	38	40	29	13	
eGFR <30 mL • min^{-1} • 1.73 m^{-2}	4	3	4	1	0	
Medical history (%)						
Hypertension	52	54	55	56	55	.49
Diabetes	25	26	28	29	27	.33
Atrial fibrillation	17	18	18	20	19	.61
COPD	20	18	21	23	21	.02
Stroke or TIA	5	4	5	6	4	.16
Medication (%)						
ACEi or ARB	93	94	93	95	95	.08
Beta-blockers	69	67	66	69	65	.28
Diuretics	87	89	88	89	89	.53
Spironolactone	41	38	37	42	40	.03
Statin	24	22	25	23	22	.15
ICD therapy (%)	7	8	7	6	6	.07

BMI, body mass index; NYHA, New York Heart Association functional class; HF, heart failure; LVEF, left ventricular ejection fraction; HR, heart rate, SBP, systolic blood pressure; SBP, diastolic blood pressure; KDOQI, Kidney Disease Outcomes Quality Initiatives, COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator.

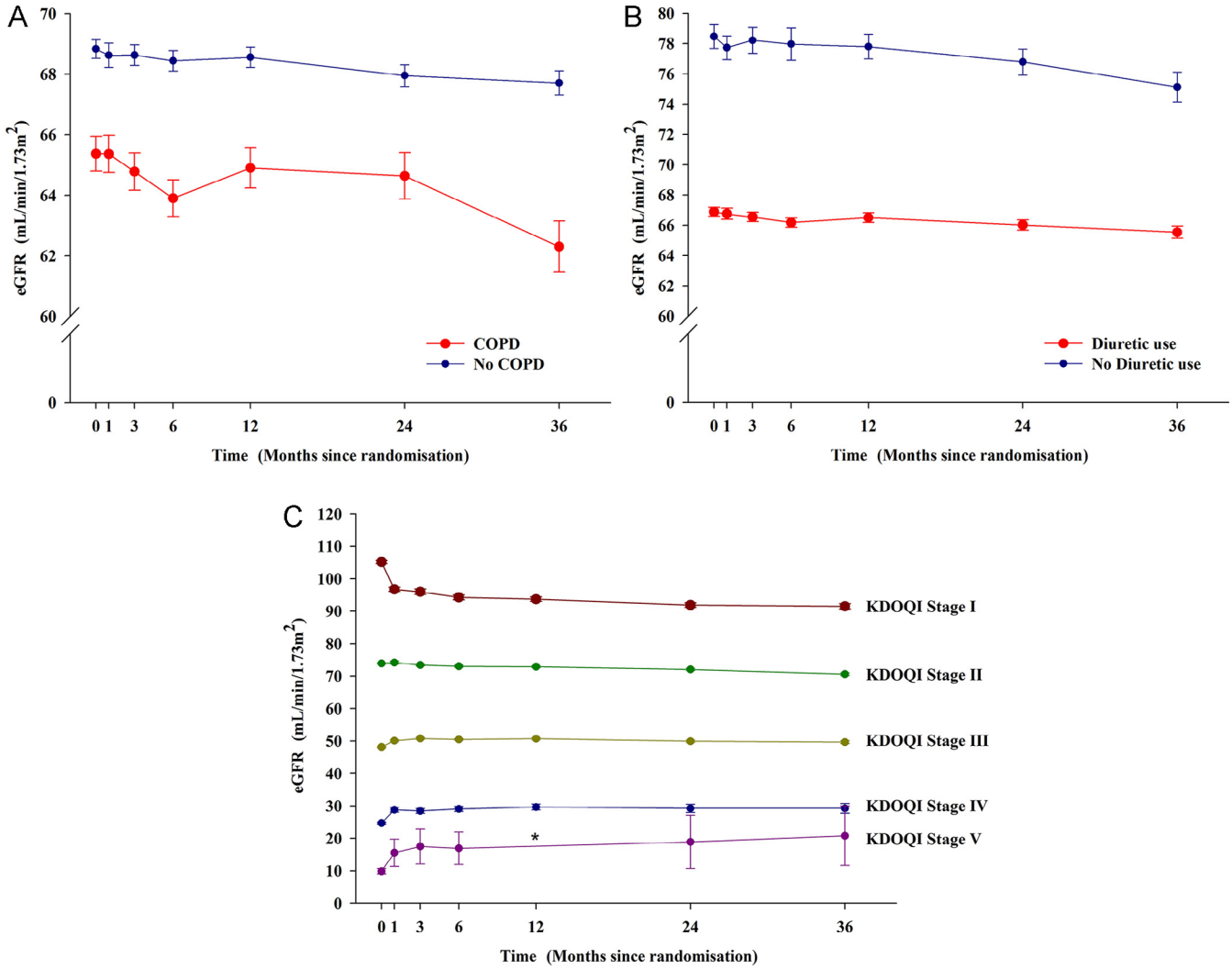

Fig. 2. (A) Change in estimated glomerular filtration rate (eGFR) in patients with and without chronic obstructive pulmonary disease (COPD) at baseline. (B) Change in eGFR in patients with and without loop diuretics at baseline. (C) Change in eGFR according to Kidney Disease Outcomes Quality Initiatives (KDOQI) stages. *Too few serum creatinine values were available at this point (12 months) for the KDOQI stage V group to allow accurate eGFR assessment for this group.

ratio [HR] 1.10 per 10 mL • min^{-1} • 1.73 m^{-2}, 95% confidence interval [CI] 1.08–1.10; $P < .001$), but the trend appeared to be nonlinear. Cox regression performed after restricted cubic splines transformation of eGFR showed a significant nonlinear component ($P < .01$), and the plot of the log-relative hazard vs eGFR indicated a clear cutoff value at an eGFR of 70 mL • min^{-1} • 1.73 m^{-2}. Above this value, changes in eGFR showed no association with the primary end point (Fig. 3; Supplemental Fig. 1).

Estimated GFR as time-varying variable showed similar associations with the primary outcome (HR 1.14, 95% CI 1.12–1.17; $P < .001$). In addition, eGFR assessed according to KDOQI classification showed a gradual increase in event rates with more severe KDOQI classes We found similar associations between eGFR/KDOQI classification and outcome for each of the individual end points (Table 2).

In addition to baseline eGFR, changes over the 1st year showed strong associations with clinical outcome. Every 10 mL • min^{-1} • 1.73 m^{-2} decrease in eGFR over the 1st year was associated with a subsequent increase in the primary end point (HR 1.10, 95% CI 1.04–1.17; $P < .001$). There was a nonlinear association between the change in eGFR in the 1st year of the study and subsequent outcome. Supplemental Fig. 2 shows the restricted cubic spline and associated HR for the change in eGFR in the 1st year. It shows a clear association between decrease in eGFR and worse clinical outcome. With the use of no change in eGFR as the reference value, patients with 15 mL • min^{-1} • 1.73 m^{-2}/year decrease had the highest risk (HR 1.22, 95% CI 1.10–1.36), followed by patients with 5 mL • min^{-1} • 1.73 m^{-2}/year decrease (HR 1.10, 95% CI 1.06–1.14). Patients with 5 mL • min^{-1} • 1.73 m^{-2}/year increase (HR 0.91, 95% CI 0.86–0.96) or 15 mL • min^{-1} • 1.73 m^{-2}/year increase (HR 0.84, 95% CI 0.75–0.95) had relatively better outcomes compared with those with stable or deteriorating renal function (Fig. 4).

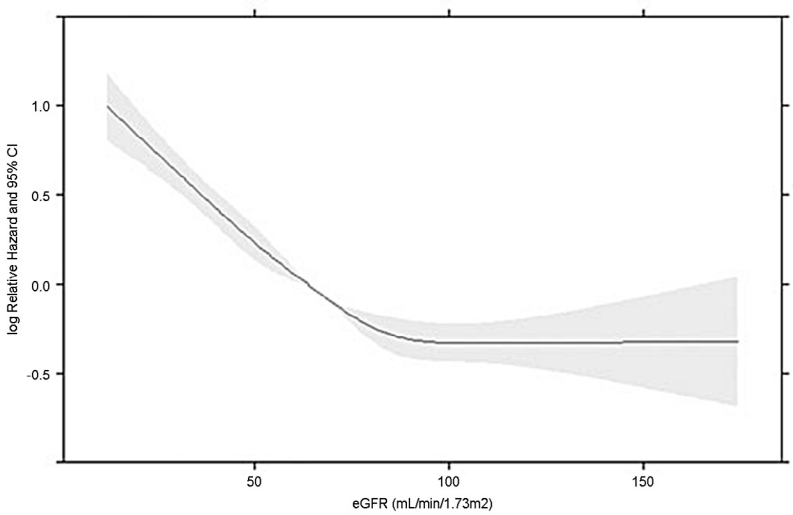

Fig. 3. Hazard ratio for estimated glomerular filtration rate (eGFR) on continuous scale.

Discussion

In patients with chronic HF included in the GISSI-HF study, changes in renal function over time were of modest magnitude. Overall, estimated GFR decreased by 2.57 mL • min^{-1} • 1.73 m^{-2}/year, and one-fourth of patients had progression of ≥1 CKD stage. Any decrease in eGFR over time was associated with strongly increased event rates.

Changes in Renal Function and Progression of CKD

Recently, research in cardiorenal interaction has shifted from assessment of baseline renal function to assessment of renal function over time, although it had long been an important research topic.[3,10]

Some analyses have given more insight into how renal function behaves during the longer time course of randomized trials. In Val-HeFT (Valsartan Heart Failure), the mean change in eGFR over the entire study period of 3 years was 2.9 mL • min^{-1} • 1.73 m^{-2} in the placebo group.[4] In EMPHASIS-HF (A Comparison of Outcomes in Patients in NYHA Functional Class II Heart Failure When Treated With Eplerenone or Placebo in Addition to Standard Heart Failure Medicines), annual decrease in eGFR was 0.066 mL • min^{-1} • 1.73 m^{-2} in the placebo group,[11] and in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Systolic Function) study eGFR decreased 5.0 mL • min^{-1} • 1.73 m^{-2} over 30 months in HF patients with reduced ejection fraction.[12] After hospitalization, eGFR seems to deteriorate faster, as one study found that eGFR decreased 7 mL • min^{-1} • 1.73 m^{-2} in the 1st 18 months after discharge.[13] In GISSI-HF, we found that estimated GFR decreased 3.7 mL • min^{-1} • 1.73 m^{-2} over 3 years. This was similar to the change of the placebo group in Val-HeFT, but substantially higher than the patients enrolled in EMPHASIS-HF. Although in GISSI-HF a minority of patients had HF with preserved ejection fraction, we did not find a significant interaction between the slope in eGFR and LVEF, suggesting that changes in these groups were similar. Importantly, the randomized treatment allocation in

Table 2. Cox Proportional Hazard Analysis

Variable	Combined End Point		CV Death		HF Hospitalization	
Baseline	Multivariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value
eGFR (per 10 mL • min^{-1} • 1.73 m^{-2} decrease)	1.10 (1.08–1.12)	<.001	1.14 (1.11–1.17)	<.001	1.10 (1.08–1.12)	<.001
KDOQI stages		<.001		<.001		<.001
Stage I (>90 mL • min^{-1} • 1.73 m^{-2})	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Stage II (60–90 mL • min^{-1} • 1.73 m^{-2})	1.16 (1.04–1.29)		1.00 (0.82–1.21)		1.19 (1.06–1.34)	
Stage III (30–60 mL • min^{-1} • 1.73 m^{-2}))	1.55 (1.38–1.75)		1.54 (1.26–1.88)		1.60 (1.41–1.81)	
Stage IV (15–30 mL • min^{-1} • 1.73 m^{-2})	2.35 (1.94–2.84)		2.59 (1.96–3.41)		2.40 (1.95–2.94)	
Stage V (<15 mL • min^{-1} • 1.73 m^{-2})	1.47 (0.69–3.13)		2.86 (1.16–7.06)		1.50 (0.66–3.37)	
Change in eGFR						
Change in eGFR in 12 mo (per 10 mL • min^{-1} • 1.73 m^{-2} decrease)	1.10 (1.04–1.17)	<.001	1.08 (1.03–1.13)	.001	1.12 (1.08–1.17)	<.001
Change in eGFR in 12 mo		<.001		.003		<.001
>15 mL • min^{-1} • 1.73 m^{-2} decrease	1.08 (0.93–1.26)		1.23 (1.01–1.51)		1.24 (1.10–1.40)	
5–15 mL • min^{-1} • 1.73 m^{-2} decrease	1.10 (0.97–1.24)		1.12 (0.94–1.34)		1.21 (1.09–1.34)	
−5 to +5 mL • min^{-1} • 1.73 m^{-2} (stable)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
5–15 mL • min^{-1} • 1.73 m^{-2} increase	0.81 (0.70–0.93)		0.82 (0.67–1.00)		0.89 (0.79–0.99)	
>15 mL • min^{-1} • 1.73 m^{-2} increase	0.89 (0.75–1.06)		0.87 (0.67–1.13)		0.90 (0.78–1.05)	

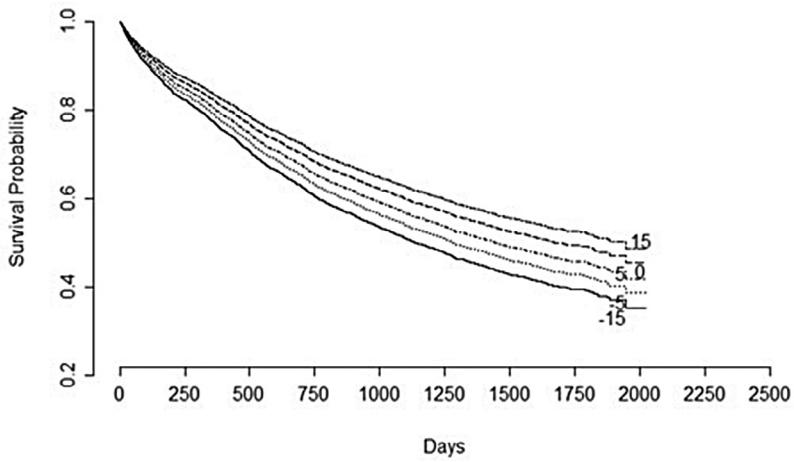

Fig. 4. Kaplan-Meier curve of change in estimated glomerular filtration rate (eGFR) in the 1st year. Numbers on lines indicate change in eGFR in mL • min^{-1} • 1.73 m^{-2} in the 1st year.

GISSI-HF did not affect change in renal function, strengthening the overall applicability of our findings. In analogy to de Silva et al, who investigated changes in CKD stages over a 6-month period and found that 19% deteriorated and 12% improved ≥1 class during this period, we evaluated changes in KDOQI stages across the study.[14] In GISSI-HF, these numbers were 25% for deterioration of ≥1 stage, and 14% for improvement of ≥1 stage. In a retrospective analysis of SOLVD (Studies of Left Ventricular Dysfunction) treatment, ~12% had a fast deterioration of eGFR (>15 mL • min^{-1} • 1.73 m^{-2}/year).[15] The figure in the 1st year of GISSI-HF was similar (15%), probably a reflection of patients with more severe HF in GISSI-HF counterbalanced by less well treated patients in SOLVD. In that particular analysis, most prominent predictors of this rapid decline were female sex, higher baseline GFR, more severe HF, and greater age. In comparison, we found that higher baseline GFR and more severe HF (as indicated by loop diuretic use) were associated with a steeper slope of eGFR change. The observation that higher baseline GFR was associated with steeper decrease in eGFR is probably a reflection of regression to the mean. Pulmonary disease was another factor associated with a stronger decrease in eGFR, but this was not investigated in SOLVD.[15] Other studies on WRF have indicated similar as well as different factors associated with change in GFR.[3,14,16,17] Overall, it seems that patients with more severe HF, greater age, and more comorbidities, such as COPD, are at greater risk for a steeper decline in GFR. This is in agreement with the present findings, where patients with COPD had a slightly more rapid decline in eGFR. One reason could be that patients with pulmonary disease are more likely to have higher right-sided filling pressures, which are now known to have a great effect on renal function. Another reason could be that COPD and renal disease share similar risk factors, such as smoking, atherosclerosis, and chronic hypoxia. Putting these changes in renal function in perspective, long-term observations in the general (healthy) population have shown that eGFR declines 0.3–1.0 mL • min^{-1} • 1.73 m^{-2}/year.[1] This suggests that the mean overall change in chronic HF patients in GISSI-HF was slightly, but probably significantly, greater compared with the general population and that a significant proportion of patients experience much larger yearly decreases in GFR compared with what could have been expected from the general population.

Changes in Renal Function and Subsequent Outcome

Lower eGFR at any time has been shown to be associated with poor outcome, and, in general, similar associations exist for deterioration of renal function, ie, WRF.[3,18,19] However, these changes in renal function have been evaluated during a very short time period, mostly in-hospital or out-of-hospital for up to 6 months. In a recent meta-analysis that pooled all different WRF definitions and different patient populations, WRF was independently associated with poor clinical outcome.[3] This was apparent in both acute and chronic HF, although it seems clear that a solitary increase in serum creatinine in acute HF without further deterioration in the clinical condition is probably clinically insignificant.[20,21] In chronic HF, the best data originate from retrospective analyses from randomized clinical trials on renin-angiotensin-aldosterone system (RAAS) inhibitors, and because of their inherent effect on renal function, they are to some extent biased.[4,11,19,22,23] However, these studies have shown that increases in serum creatinine during initiation of RAAS inhibitors are not associated with poor outcome. Importantly, these trials had safety protocols, where therapies should be down-titrated or discontinued when creatinine rose too high, which could have influenced these associations. Furthermore, in our present analysis from GISSI-HF, 93% were on stable angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy and more than one-third (39%) on spironolactone.

Only limited data exist on changes in renal function and outcome in cohorts other than the mentioned randomized trial. De Silva et al showed that 6-month mortality was ~5 times higher in patients with concomitant severe baseline renal dysfunction and WRF compared with patients with normal baseline renal function and no WRF.[14] In a retrospective

analysis of patients recently discharged from hospital, WRF directly after admission or from 6–12 months after admission was associated with significantly increased mortality rates.[13] In the present retrospective analysis of GISSI-HF, we found that any deterioration in renal function during the 1st year was associated with strongly increased event rates. Every 10 mL • min^{-1} • 1.73 m^{-2} decrease in eGFR was associated with a 10% increase in the combined end point. This was further supported by the finding that improvement in renal function was associated with significantly better outcomes compared with patients with relatively stable renal function, as well as the finding that eGFR evaluated with the use of time-varying analysis showed similar results. Overall, our findings strongly suggest that any deterioration in renal function over a moderately long period—whatever the cause—is associated with poorer clinical outcome, even if the decrease seems clinically insignificant. This suggests that routine evaluation of renal function in each HF patient is vital for the assessment of clinical status and mortality/morbidity risk. It also may help in selecting patients where deterioration of renal function serves as a proxy of the progression of the disease and who need more advanced HF therapy. This may also be where the clinical relevance of serial assessment of renal function may come into play: it gives important information on the (change in) severity of heart failure, an indication of the subsequent prognosis, and, with the present data as information on the "normal" change in eGFR, may give information on more or less than expected changes in eGFR over time. Whether or not this should result in more investigations and/or change of therapy should be determined on a case-by-case basis and cannot be deducted from the present analysis.

Study Limitations

This analysis of GISSI-HF is retrospective in nature, consisting of data gathered in a trial population, and should therefore be seen as hypothesis generating. The analysis can only indicate associations and in no way can imply causality. Our results are also observational in nature. Decisions by clinicians that could have affected renal function and outcome were not taken into account, and this could have influenced our analyses. Other significant limitations are estimation of GFR rather than measurement, but the formula used in our present analysis has been validated in chronic HF patients with acceptable accuracy. We used the simplified MDRD formula, because this was the formula used in the primary analysis of GISSI-HF. Although the Chronic Kidney Disease–Epidemiology Collaboration formula probably gives a better estimate of GFR, differences in the changes in eGFR between the 2 formulas are likely small. Although urinary albumin excretion was available in a subset of patients, it was available at different time points for each patient and therefore not included in this analysis. Major strengths of the present analysis are the large population size and the noninterference of randomized treatment with renal function, as well as the long follow-up time.

Conclusion

Estimated GFR in chronic HF patients in GISSI-HF showed a modest decrease over ≥3 years, although a significant proportion of patients experienced much greater decreases in eGFR. Baseline renal impairment, particularly (modest) decreases in eGFR over time, was associated with significantly increased event rates. The results suggest that evaluation of renal function should be part of the routine clinical work-up of every chronic HF patient.

Disclosures

None.

Appendix: Supplementary Data

Supplementary data related to this article can be found at at doi:10.1016/j.cardfail.2016.09.006.

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